REMARKS

Claims 2-34 were pending in the instant application. Claims 18-34 are pending and withdrawn from consideration. Claims 2 and 3 have been amended to specify that the modified base is located at an internal residue of the antisense strand. Support for this amendment is found at least, for example, on page 14, lines 16-23 and in Figure 4 of the application as filed. Accordingly, upon entry of the amendments presented herein, claims 2-34 will remain pending and claims 18-34 will remain pending and withdrawn.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any other Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

I. Rejection of claims 2-8 and 10-17 under 35 U.S.C §103(a)

A. Summary of Examiner's position

The Examiner has rejected claims 2-8 and 10-17 under 35 U.S.C §103(a) as being unpatentable over Ecker *et al.* (U.S. Patent No. 5,965,722) in view of ten Asbroek *et al.* (Nucleic Acid Research 2000, Vol. 28: 1133-1138), Hojo *et al.* (Eur. Respir. J., 1998), Hammond *et al.* (Nature Reviews Genetics, 2001), Bass *et al.* (Nature, 2001) and Tuschl *et al.* (WO 02/44321) for the reasons set forth in the Office Action mailed April 1, 2009.

Briefly, the Examiner relies on Ecker *et al.* for teaching that "antisense compounds comprising modified nucleotide bases increase the affinity for such base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes." The Examiner further relies on Ecker *et al.* for teaching that "a single nucleotide mutation is responsible for mutated Ras protein expression," and that "incorporation of a 2,6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene."

The Examiner relies on ten Asbroek *et al.* for teaching the use of "antisense compounds targeted to one mutatnt allele of a pair that is vital to cell growth and viability of the cancer cell."

The Examiner acknowledges that Ecker *et al.* and ten Asbroek *et al.* "do not teach siRNA targeted to a mutated gene and do not teach the point mutation is an adenine or thymine."

The Examiner further relies on Hammond *et al.* and Bass *et al.* for teaching the superior efficacy of RNAi, and on Hojo *et al.* for teaching that point mutations of the p53 gene are commonly an adenine or a thymidine.

Finally, the Examiner relies on Tuschl *et al.* for teaching that "siRNAs represent a new alternative to antisense or ribozyme therapeutics," and also that "siRNA may contain at least one modified analogue, such as... 5-bromouracil or 5-iodouracil," and furthermore that "nucleotides in the center of the siRNA strand are important specificity determinants" and therefore, "siRNA duplexes can disciminate between mutant and polymorphic alleles..."

The Examiner alleges that "Ecker *et al.* and ten Asbroek *et al.* provide evidence that one of skill in the art would have had a reasonable expectation of success at targeting and reducing expression of a mutant target gene... given that Tuschl *et al.* teach how to make and use any siRNA targeted to any gene," and given that "Hammond *et al.* and Bass *et al.* teach siRNA are preferred over antisense compounds, one would have had a reasonable expectiation of success at making a siRNA targeted to a mutated gene." The Examiner concludes that the invention would have been *prima facie* obvious to one of skill in the art.

B. Applicant's Response

i. *References fail to teach or suggest each and every element of the claimed invention*

The test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Intl Co. v. Telefler Inc.,* 127 S. Ct. 1727 (2007). *Takeda Chem. Indus., Ltd. v. Alpharma Pty., Ltd.,* 2007 U.S. App. LEXIS 15349, at *13 (Fed. Cir. 2007). "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying a 'reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Id.* at *1344 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR,* 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.*

Applicant respectfully traverses this rejection, at least for the reasons set forth in Applicant's response filed October 2, 2007, which are partially reiterated below, and augmented

with new arguments. Applicant maintains that the cited references, alone and in combination, fail to teach or suggest each and every element of the present invention as recited in the claims herein. Furthermore, certain references cited by the Examiner teach away from the instant invention.

ii. *Summary of claimed invention*

Claim 2 (and the claims that depend therefrom) is directed to an siRNA capable of single nucleotide discrimination between a first and second allele, the first allele having 1, 2, 3 or more point mutations relative to the second allele, wherein the siRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in the first allele, and wherein the modified base is capable of enhancing binding interactions between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele. Claim 3 (and the claims that depend therefrom) is drawn to an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a sequence homologous to a region of a mutant allele encoding a gain-of-function mutant protein, said region comprising one or more point mutations, and wherein the antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations, such that the siRNA directs allele-specific cleavage of a mRNA encoded by the mutant allele.

iii. *Analysis of cited art with respect to motivation: Ecker et al.*

The teachings of Ecker *et al.* are directed to antisense DNA oligonucleotides for specific inhibition of expression of a mutant form of the Ras gene. In particular, Ecker *et al.* teach that antisense phosphorothioate DNA oligononucleotides in which 2,6-(diamino)adenine is positioned complementary to the uracil of the mutated codon 12 of activated Ras stabilizes hybridization of the modified antisense oligonucleotide to the activated Ras gene and increases specificity for the mutant target. Ecker *et al.* fail to teach or suggest any RNA oligonucleotide, let alone an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in a mutant allele. Ecker *et al.* also fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises 5-bromo-uridine or 5-iodo-uridine positioned opposite a point mutation of adenine in a mutant allele, as required by claim 6. Ecker *et al.* also fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense

strand comprises 2,6-diaminopurine positioned opposite a point mutation of thymine in a mutant allele, as required by claim 8.

One skilled in the art would not have had the motivation to extend the teachings of Ecker *et al.* to siRNA molecules, since nothing in the teachings of Ecker *et al.* suggests a need in the art for an alternate molecule to an antisense molecule for the specific inhibition of expression of a mutant gene. Moreover, Ecker *et al.* teach away from the claimed invention. In particular, Ecker *et al.* teach that RNase H is an endonuclease that cleaves the RNA strand of RNA:DNA duplexes and that activation of this enzyme by an antisense DNA oligonucleotide results in cleavage of the RNA target (column 4, lines 37-41). Accordingly, Ecker *et al.* teach that preferred antisense oligonucleotides are DNA oligonucleotides, *e.g.*, having phosphodiester or phosphorothioate linkages, since they activate the cleavage of target RNA by RNase H and thereby "greatly enhance the ability of antisense oligonucleotides to inhibit target RNA expression" (column 4, lines 28-42). Accordingly, one would not have been motivated, based on the teachings of Ecker *et al.*, to substitute the antisense DNA oligonucleotides of Ecker *et al.* with an siRNA, since Ecker *et al.* teach that DNA oligonucleotides are preferred for inhibition of target RNA expression. In the Office Action of December 11, 2007, the Examiner dismissed this argument, stating that "whether or not the siRNA would activate RNase H is irrelevant to the overall motivation to inhibit gene expression." Applicants respectfully disagree, and contend that a reference can not simultaneously teach against and motivate.

iv. *Analysis of cited art with respect to motivation: ten Asbroek et al.*

The teachings of ten Asbroek *et al.* fail to make up for the deficiencies of Ecker *et al.* The ten Asbroek reference teaches antisense compounds useful for the treatment of cancer, due to their ability to discriminate between mutant and wild type genes exhibiting single nucleotide polymorphism. ten Asbroek *et al.* fail to teach or suggest any RNA oligonucleotide, let alone an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in a mutant allele. ten Asbroek *et al.* also fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises a modified nucleotide positioned opposite a point mutation in a mutant allele, much less a 5-bromo-uridine or 5-iodo-uridine positiond opposite an adenine, as required by claim 6, or a 2,6-diaminopurine positioned opposite a thymine, as required by claim 8.

v. *Analysis of cited art with respect to motivation: Hammond et al and Bass et al.*

The teachings of Hammond *et al.* and Bass *et al.* fail to make up for the deficiencies of Ecker *et al.* Both the Hammond and Bass references merely teach that RNAi is more "robust" than antisense technologies. Both the Hammond and Bass references fail to teach or suggest siRNAs comprising any modified nucleotides, let alone modified nucleotides positioned opposite point mutations in mutant alleles, nor do these references teach that such modified siRNAs may be used to achieve single nucleotide discrimination between a wild type and mutant allele or direct allele-specific cleavage of mRNA encoded by a mutant allele, as required by the claims.

vi. *Analysis of cited art with respect to motivation: Hojo et al*

The teachings of Hojo *et al.* also fail to make up for the deficiencies of Ecker *et al.* Hojo *et al.* teach that pulmonary fibrosis is associated with overexpression of p53, and that such p53 overexpression is often associated with G: C to A:T and A:T to G:C transitions. Hojo *et al.* is devoid of any teaching regarding the use of siRNAs, or any other molecule, to direct the cleavage of a mutant gene (e.g., mutant p53 as described by Hojo et al.), let alone siRNAs comprising a modified nucleotide positioned opposite the specific point mutations in a mutant allele, as presently claimed. Hojo *et al.* fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises 5-bromo-uridine or 5-iodouridine positioned opposite a point mutation of adenine in a mutant allele, as required by claim 6, or comprises 2,6-diamizzopurine positioned opposite a point mutation of thymine in a mutant allele, as required by claim 8.

vii. *Analysis of cited art with respect to motivation: Tuschl et al*

The teachings of Tuschl *et al.* also fail to make up for the deficiencies of Ecker *et al.* Tuschl *et al.* teach that siRNA molecules containing modified nucleotides are useful for mediating RNA interference, however, Tuschl *et al.* fail to teach or suggest the incorporation of a modified base into an siRNA for the purpose of enhancing affinity for a mutant allele versus a wild type allele. As set forth in Applicant's previous Response filed February 15, 2007, Tuschl *et al.* fail to teach both the structure and the function imparted by that structure of the presently claimed siRNAs. In particular, Tuschl *et al.* fail to teach or suggest the specific positioning of a modified base in the antisense strand of an siRNA opposite a point mutation in the target mRNA of a mutant allele, let alone that such siRNAs can be used for single nucleotide discrimination

between a wild type and mutant allele or to direct allele-specific cleavage of mRNA encoded by a mutant allele, as required by the pending claims.

More importantly, Tuschl *et al.* teach away from the instant invention, by stating:

> [n]ucleotides in the centre of the siRNA, located opposite the target RNA cleavage site, are important specificity determinants. (page 50, lines 10-12)
>
> and then:
>
> [in] an especially preferred embodiment of the present invention the RNA molecule may contain at least one modified nucleotide analogue. The nucleotide analoge may be located at positions where the target-specific activity, *e.g.* the RNAi mediating activity is not substantially effected, *e.g.* in a region at the 5'-end and/or the 3'-end of the double stranded molecule. (page 5, lines 15-20)

In contrast, Applicant teaches that:

> modified siRNAs of the invention preferably comprise one or more modified nucleobases, wherein the nucleobases are capable of enhancing the specificity of the siRNA, *e.g.* to a target mutant allele as compared to a corresponding wild-type allele. (page 9, lines 11-13 of the application as filed)

Importantly, the siRNA molecules of the instant invention can be modified at internal residues to achieve specificity (page 14, lines 16-18 of the application as filed). Tuschl *et al.* clearly teach against this critical aspect of the instant invention and as such, Applicants would not find teaching, suggestion, or motivation in this reference.

viii. *Analysis of cited art with respect to motivation: Summary*

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (MPEP §2143.01) One skilled in the art would not have found the suggestion or motivation to combine the teachings of the cited art to arrive at the present invention. In fact, elements of the cited art clearly teach the undesirability of such a combination.

ix. *Analysis of cited art with respect to reasonable expectation of success*

a. *Different mechanisms*

Even if the motivation to extend the teachings of Ecker *et al.* to an RNAi based approach were to exist, (which it does not), the skilled artisan would have had no reasonable expectation of success in using the Ecker methodology. In the Office Action dated April 1,

2009, the Examiner states "given that both the antisense compound and siRNA compound are designed to recognize a target gene through complementarity to the target gene, [one] of skill in the art would... have a reasonable expectation of success at being able to initiate gene silencing of a mutant target gene using siRNA." Applicant respectfully disagrees, and contends that the skilled artisan would not reasonably expect success based on a superficial similarity when sophisticated mechanistic insight was available.

The skilled artisan would have readily understood, at the time the instant application was filed, that the results obtained for targeting an antisense molecule containing modified nucleotides to a mutated gene (as taught by Ecker *et al.)* could not be extrapolated to the targeting of an siRNA molecule to a mutant allele (*e.g.*, wherein the siRNA comprises an antisense strand having a modified nucleotide positioned opposite the point mutation of the mutant allele) with any reasonable expectation of success because the molecules operate through very different cellular mechanisms. In particular, the state of the art at the time of filing recognized that an antisense oligonucleotide inhibits transcription and/or translation of target genes by base-pairing with the target sequence and blocking translocation of the transcription/translation machinery. In contrast, RNAi was recognized to involve the assembly of the RNA molecule with protein components to form a nuclease complex, RNAi-Inducing Silencing Complex (RISC), that RISC utilizes an active mechanism to search for the homologous mRNA target and ultimately mediates degradation of the mRNA target.

Given the distinct mechanism of RNAi as compared to that of antisense technology, the skilled artisan would not, based on the current state of the art and the teachings of the cited references, have had any reasonable expectation of success in making and using an siRNA as claimed.

b. Difficulty of single-nucleotide discrimination

Moreover, one skilled in the art would have had no reasonable expectation that single nucleotide discrimination between a wild type and mutant allele obtained with an antisense oligonucleotide could be extrapolated to an siRNA having a single modified nucleotide positioned opposite the point mutation of a mutant gene. This is because, as noted by the Examiner, and as evidenced by the Hammond *et al.* and Bass *et al.* references, RNAi is a remarkably efficient means of effecting gene silencing as compared to antisense technology. As previously set forth in the Response filed October 2, 2008, at the time of filing of the instant application there were numerous reports that RNAi technology could tolerate single-base

mismatches between the antisense strand of the siRNAs and the target RNA. Thus, one skilled in the art would not have had a reasonable expectation of success that an siRNA could be used to achieve single nucleotide discrimination. Indeed, there is nothing in Ecker *et al.* that teaches or even remotely suggests that a wild type gene would be resistant to RNAi. Ecker *et al.* merely teach that the wild type ras gene, as compared to mutant ras, is resistant to the relatively inefficient antisense silencing technology of the reference. Notably, the siRNA methodology of the instant invention significantly silences a target mutant gene as compared to the corresponding wild type gene.

In the Office Action dated December 11, 2007, the Examiner stated that "Applicant has not provided any evidence to the contrary supporting their conclusion that siRNA are incapable of allele specific silencing and are invited to do so." The Examiner points to Xu *et al.* as evidence that siRNAs are capable of allele specific gene silencing.

The Xu reference notwithstanding, Applicant stresses that whether single nucleotide specificity was achievable with RNAi technology had not been resolved by those skilled in the art at the time of the invention. For example, Boutla *et al.* (Boutla A *et al.*, *Current Biology,* 11: 1776-80 (2001), previously made of record in the Information Disclosure Statement filed November 20, 2007), published prior to the priority date of the application, indicated that single nucleotide discrimination was beyond the limits of siRNA technology. Boutla *et al.* reported that siRNAs differing from the sequence of their target mRNA at one or more nucleotides retained efficacy, indicating that the siRNA technology did not require perfect sequence complementarity of the siRNA with the mRNA to silence its expression. Specifically, a reference siRNA with full complementarity to *Notch* mRNA exhibited 93% penetrance (measure of silencing), while three different single-nucleotide mutants exhibited values of 81%, 88%, and 93% penetrance, leading Boutla *et al.* to conclude that "a perfect match to the target RNA is not necessary to initiate the RNAi response" (page 1779). In the Office Action of April 1, 2009, the Examiner acknowleges the Boutla *et al.* teaching that "siRNA with single nucleotide mismatches were still capable of inducing RNAi in whole organism," but qualifies this point by paraphrasing the authors that "this observation will require a more detailed analysis..." Applicant takes the position that the Boutla *et al.* results are indicative of the state of the art at the time of the instant invention, and that at this time reliable and efficient differentiation of single-nucleotide polymorphs was generally beyond the capability of the art.

Applicant finds additional evidence of the state of the art at the time of the invention in the work of Holen *et al.* (Holen T. *et al.*, *Nucleic Acids Research,* 30(8): 1757-66 (2002),

previously made of record in the Information Disclosure Statement filed January 12, 2009). Holen *et al.* synthesized siRNA to target sites within the mRNA of human tissue factor (TF), and observed that the wild-type siRNA *hTF167i-wt* exhibited 80% silencing capability. By comparison, the single-nucleotide mutant siRNA *hTF167i-M1*exhibited 65% silencing capability, leading the authors to conclude that "RNAi to a certain degree tolerates siRNA:mRNA mismatches" (page 1765) despite the fact that the mismatches "were chosen to be maximally disruptive" (page 1763).

Further evidence of the unpredictable state of the art at the time of the invention is found in the work of Jacque *et al.* (Jacque, J-M. *et al.*, *Nature*, 418: 435-438 (2002), made of record in the present Amendment in Response as Exhibit A). Jacque *et al.* directed siRNA duplexes against several regions of the HIV-1 genome, including the viral long terminal repeat (*LTR*). *LTR* was targeted with both the wild-type siRNA *TAR* and the single-nucleotide mutant *MTAR*, both of which suppressed reverse transcription activity to nearly the same extent (page 435, Figure 1b).

Yu *et al.* (Yu, J-Y. *PNAS*, 99: 6047-6052 (2002), previously made of record in the Information Disclosure Statement filed November 20, 2007) observed that hairpin RNA (shRNA) possessing a single mismatch relative to the *luc-GFP* target silenced the reporter to nearly the same extent. Any difference was within the margin of error (page 6048, Figure 2c).

Finally, Hamada *et al.* (Hamada, M., *Antisense and Nucleic Acid Drug Development*, 12: 301-309 (2002), made of record in the present Amendment in Response as Exhibit B) found that wild-type siRNA targetting *JDP-2* exhibited reporter silencing of 60%, while the single-nucleotide mutant siRNA silenced reporting by 30%. The authors comment that the limited RNAi effects observed by themselves, as well as Elbashir *et al.* (Elbashir, S.M., *EMBO*, (2001), previously made of record in the Information Disclosure Statement filed January 12, 2006) "were not completely in accord with the findings of more recent studies, possibly because of the different conditions used" (page 305), thereby acknowledging the uncertainty prevailing in contemporary research.

Collectively, the preceding references suggest that the effect of single-nucleotide mutations on RNAi efficiency was unpredictable at the time of the invention, and that one skilled in the art would have had no reasonable expectation that allele-specific gene silencing would be successful.

C. Summary

In summary, the Examiner has failed to point to any teaching in the Ecker *et al.,* Hojo *et al.,* Hammond *etal.,* Bass *et al.* and Tuschl *et al.* references that would compel one of ordinary skill in the art to make the claimed invention with any reasonable expectation of success. The prior art must suggest "to those of ordinary skill in the art that they *should* make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the *reasonable expectation of success* must be founded *in the prior art, not in the applicant's disclosure* (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

II. Rejection of Claims 2-17 under 35 USC § 103(a)

A. Summary of Examiner's position

The Examiner has newly rejected claims 2-17 under 35 U.S.C. §103(a) as being obvious over Klug *et al.* (European Journal of Physiology, 2001), Ecker *et al.* (US Patent No. 5,965,722), Hammond *et al.* (Nature Reviews Genetics, 2001), Bass *et al.* (Nature, 2001) and Tuschl *et al.* (WO 02/44321).

The Examiner relies on Klug *et al.* to teach an antisense compound that is selective against the G93A point mutation in an *SOD1* gene responsible for ALS, as compared to the wild-type gene. The Examiner acknowledges that Klug *et al.* "do not teach siRNA targeted to a gene correlated with a disease selected from *ALS, Huntington's disease, Alzheimer's disease or Parkinson's Disease...*"

The Examiner relies on Ecker *et al.,* for the reasons set forth above. The Examiner acknowledges that Ecker *et al.* "do not teach siRNA targeted to a gene correlated with a disease selected from *ALS, Huntington's disease, Alzheimer's disease or Parkinson's Disease...*"

The Examiner further relies on Hammond *et al,* Bass *et al.,* and Tuschl *et al.* for the reasons set forth above.

B. Applicant's Response

i. References fail to teach or suggest each and every element of the claimed invention

Applicant respectfully traverses this rejection for the reasons set forth above. Applicant maintains that the cited references, alone and in combination, fail to teach or suggest each and every element of the present invention as recited in the claims herein. Furthermore, certain references cited by the Examiner teach away from the claimed invention.

ii. *Summary of claimed invention*

Claim 2 (and the claims that depend therefrom) is directed to an siRNA capable of single nucleotide discrimination between a first and second allele, the first allele having 1, 2, 3 or more point mutations relative to the second allele, wherein the siRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in the first allele, and wherein the modified base is capable of enhancing binding interactions between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele. Claim 3 (and the claims that depend therefrom) is drawn to an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a sequence homologous to a region of a mutant allele encoding a gain-of-function mutant protein, said region comprising one or more point mutations, and wherein the antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations, such that the siRNA directs allele-specific cleavage of a mRNA encoded by the mutant allele.

iii. *Analysis of cited art: Klug et al.*

The teachings of Klug *et al.* comprise antisense DNA oligonucleotides that are selective for an *SOD1* mutant responsible for ALS. Klug *et al.* fail to teach or suggest any RNA oligonucleotide, let alone an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises a modified base positioned opposite at least one point mutation in a mutant allele. Nothing in the teachings of Klug *et al.* suggests a need in the art for an alternate molecule to an antisense molecule for the specific inhibition of expression of a mutant gene, let alone an siRNA. Thus, based on the teachings of Klug *et al.,* one would not be motivated to seek alternate molecules to antisense for specific mutant gene silencing. Even if the motivation to extend the teachings of Klug *et al.* to an RNAi-based approach were to exist, (which it does not), one of ordinary skill in the art would have had no reasonable expectation of success, due to his awareness of the mechanistic differences between the two processes, set forth above.

The Ecker *et al.*, Hammond *et al.*, Bass *et al.* and Tuschl *et al.* references are all traversed for the reasons set forth above (pages 8-11 of the present response).

Moreover, Applicant stresses that whether single nucleotide specificity was achievable with RNAi technology had not been resolved by those skilled in the art at the time of the invention. As detailed above, the Boutla *et al.*, Holen *et al.*, Jacque *et al.*, Hamada *et al.*, and

Elbashir *et al.* references collectively suggest that the effect of single-nucleotide mutations on RNAi efficiency was unpredictable at the time of the invention, and that one skilled in the art would have had no reasonable expectation that allele-specific gene silencing would be successful.

C. Summary

In summary, the Examiner has failed to point to any teaching in the Klug *et al.,* Ecker *et al.,* Hojo *et al.,* Hammond *etal.,* Bass *et al.* and Tuschl *et al.* references that would compel one of ordinary skill in the art to make the claimed invention with any reasonable expectation of success. The prior art must suggest "to those of ordinary skill in the art that they *should* make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the *reasonable expectation of success* must be founded *in the prior art, not in the applicant's disclosure* (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

III. Rejection of Claims 2-17 under 35 USC § 103(a)

A. Summary of Examiner's position

The Examiner has newly rejected claims 2-17 under 35 U.S.C. §103(a) as being obvious over Xu *et al.* (US 2004/0192629, cited on PTO Form 892 filed 11/15/2005) and Ecker *et al.* (US Patent No. 5,965,722).

By way of response, Applicant asserts that the Xu *et al.* application and the instant application were, at the time the invention of the instant application was made, owned by the University of Massachusetts.

The Ecker *et al.* reference is traversed for reasons set forth above (pages 8-9 of the present response).

In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

SUMMARY

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. UMY-041RCE2 from which the undersigned is authorized to draw.

Dated: October 1, 2009

Respectfully submitted,

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